PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: STEVEN L. HIGHLANDER
FULBRIGHT & JAWORSKI, L.L.P.
600 CONGRESS AVENUE
SUITE 2400
AUSTIN, TEXAS 78701

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year): 12 JAN 2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION	
UTFC:660-WO		
International application No.	International filing date (day/month/year)	Priority Date (day/month/year)
PCT/US01/32510	17 OCTOBER 2001	17 OCTOBER 2000

Applicant
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Alicia D. Roberts for GOLLAMUDI S KISHORE
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/416 (July 1992)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference UTFC:660-WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US01/32310	International filing date *(day/month/year)* 17 OCTOBER 2001	Priority date *(day/month/year)* 17 OCTOBER 2000
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 9/127 and US Cl.: 424/450		
Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13 MAY 2002	24 SEPTEMBER 2003
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Felicia D. Roberts for GOLLAMUDI S KISHORE Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/32310

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-101, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 102-112, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/32310

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 58

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 58 are so unclear that no meaningful opinion could be formed *(specify)*.

Claim 58 depends from itself and therefore, improper under PCT Rule 6.4 (a).

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/32310

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	2-3, 5-12, 42-57 & 59-130	YES
	Claims	1, 4 & 13-41	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-57 & 59-130	NO
Industrial Applicability (IA)	Claims	1-57 & 59-130	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 4 and 13-41 lack novelty under PCT Article 33(2) as being anticipated by WO 93/13751.

WO 93/13751 discloses the claimed method of admixing a retinoid, DMPC, t-butanol and water (col. 6, line 15 through col. 7, line 48, Examples and claims).

Claims 2-3, 42-45, 49-57 and 59-60 lack an inventive step under PCT Article 33(3) as being obvious over WO 93/13751 cited above in view of ULUKAYA et al(Cancer Treatment Reviews, 25, pp. 229-235, 1999).

As discussed above, WO discloses a method of preparation of liposomes made from the claimed combination of components. Although the invention is exemplified using retinoic acid, according to WO page 4, lines 19-25, the term includes all retinoids. WO however, does not specifically teach 4 hydroxyphenyl retinamide.

ULUKAYA et al while disclosing the relationship between 4 hydroxyphenyl retinamide and cancer, teaches that this retinoid has fewer side effects compared to naturally occurring retinoids and that it seems to induce apoptosis via different pathway from classical retinoids (note the abstract).

The use of 4-hydroxyphenyl retinamide as the specific retinoid in the teachings of WO would have been obvious to one of ordinary skill in the art since WO teaches the use of any retinoid and ULUKAYA et al teach that this retinoid has fewer side effects compared to naturally occurring retinoids and induces apoptosis via different pathway from classical retinoids.

Claims 5-9 and 46-48 lack an inventive step under PCT Article 33(3) as being obvious over WO 93/13751 cited above in view of ULUKAYA et al(Cancer Treatment Reviews, 25, pp. 229-235, 1999), further in view of UNGER et al (US 5,542,935).

The teachings of WO and ULUKAYA et al have been discussed above. What is lacking in the liposomal compositions of WO is the inclusion of a polymer linked lipid and targeting agents.

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

UNGER et al while disclosing liposomal compositions containing therapeutic agents which include anti-cancer agents teaches that the inclusion of polymer linked lipids (PEG-lipid) increases the stability of the liposomes (col. 19, lines 24-39; col. 24, lines 25-42). UNGER et al further advocate the use of targeting agents in order to reach the target site quickly since the circulation time of the liposomes is short (col. 20, lines 32-47).

The inclusion of polymer linked lipids and targeting agents in the liposomes of WO would have been obvious to one of ordinary skill in the art since such an inclusion would lead to stable liposomes and reach the target site quickly as taught by UNGER et al.

Claims 4, 10-12, 45, 49-51, 57, 59-60 lack an inventive step under PCT Article 33 (3)as being obvious over WO 93/13751 cited above in view of MINTON et a; (5,008,291) or ZELIGS (6,093,706) by themselves OR vice versa: that is, MINTON et al (5,008,291), or ZELIGS (6,093,706) in view of WO 93/13751.

As pointed out above, WO discloses a method of treatment of cancer using liposomal retinoid. The liposomes are made from the claimed combination of dimyristoyl phosphatidyl choline and the intercalation promoter, soybean oil. Although in WO, the invention is exemplified using retinoic acid, according to WO on page 4, lines 19-25, the term includes all retinoids.

MINTON et al teach that a combination method for achieving a very high degree of chemotherapeutic activity through a synergistic combination of a low suboptimal dose of calcium glucarate (anti-carcinogen) and a suboptimal dose of 4-hydroxyphenyl retinamide. One of the cancers studied is mammary cancer (abstract; col.4, line 23 through col. 6, line 41; Examples). What is lacking in MINTON et al is the use of liposomes as the sustained release carriers for the combination. However, MINTON et al on col. 13, lines 17 and 18 suggests the use of sustained or continuous release formulations.

ZELIGS teaches a combination treatment of diseases such as squamous cell carcinoma using 4-hydroxyphenyl retinamide and dehydroepiandrosterone. The combination is administered in the form of liposomes (abstract, col. 5, line 28; col. 6, line 60; Example 3; claims 46 and 55). What is lacking in ZELIGS's liposomes is the use of DMPC as the phospholipid and the inclusion of soybean oil.

It would have been obvious to one of ordinary skill in the art to use 4- hydroxyphenyl retinamide as the specific retinoid in the teachings of WO since WO teaches the use of any retinoid and the references of MINTON et al and ZELIGS show the effectiveness of this retinoid in combination with other active agents which includes synergism as noted from Minton. Alternately, the use of liposomes containing DMPC and soybean oil of WO as the sustained release carriers for the formulations of MINTON et al, or Zeligs would have been obvious to one of ordinary skill in the art since this combination of DMPC and the intercalation promoter, soybean oil is very effective for the delivery of retinoids in cancer treatment process as taught by WO.

Claims 61-130 lack an inventive step under PCT Article 33 (3) as being obvious over WO 93/13751 cited above in view of MINTON et a; (5,008,291) or ZELIGS (6,093,706) by themselves OR vice versa: that is, MINTON et al (5,008,291), or ZELIGS (6,093,706) in view of WO 93/13751 as set forth above, further in view of MARTH et al (Int. J. Cancer).

The teachings of WO, MINTON et al, ZELIGS have been discussed above. What is lacking in these references is the use of the retinoid in combination with agents which increase the levels of Nitric oxide (NO).

MARTH et al disclose that the combination of retinoids and interferon gamma (IFN gamma) (increases the level of NO) results in an synergistic amplification of anti-proliferative effect of IFN gamma (abstract).

It would have been obvious to one of ordinary skill in the art to use retinoids, the claimed retinoid, fenretinide in particular in combination with an NO inducer such as IFN gamma with a reasonable expecation of success since the references of MINTON et al and ZELIGS show synergistic effect of this retinoid in combination with other active agents and the reference of MARTH et al shows the synergistic effect of retinoic acid in combination with IFN gamma.

Claims 2-3, 5-12, 42-57 and 59-130 meet the criteria set out in PCT Article 33(2), because the prior art does not specif ically teach liposomes containing the claimed retinoid and the other components of the liposomes and the combination with other ative agents. Claims 1-57 and 59-130 meet the criteria set out in PCT Article 33 (4) since the invention finds its utility in the treatment of cancer.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

---------- NEW CITATIONS ----------

US 5,010,107 A (MINTON et al) 23 APRIL 1991, see columns 2-8 and claims.

US 5,542,935 A (UNGER et al) 06 AUGUST 1996, see col. 19, line 24 through col 26, line 33.

PATENT COOPERATION TREATY

PCT

NOTE ON INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No.	Applicant's or agent's file reference	Date of informal communication *(day/month/year)*
PCT/US01/32310	UTFC:660-WO	24 SEPTEMBER 2003

Applicant
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

Communication	Participants			
☐ by telephone		☒ identity checked	☐ authorization checked	☐ personally known
☐ personal	☒ Applicant:	BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		
	☒ Agent:	Steven Highlander		
	☒ Examiner(s):	GOLLAMUDI S KISHORE		

Summary of communication:

An authorization for sending 409 instead of 408 was discussed. The attorney agreed for a 409.

☐ ~~An extension of time limit is granted (Form PCT/IPEA/427).~~

☐ A copy of this note is being sent to the applicant with Form ~~PCT/IPEA/420.~~ PCT/IPEA/~~424~~409

Applicant/Agent	Authorized officer of IPEA/US
Steven Highlander	Felicia D. Roberts for GOLLAMUDI S KISHORE Telephone No. (703) 308-1235

Form PCT/IPEA/428 (July 1992)*

Image AF/1600

FULBRIGHT & JAWORSKI L.L.P.
A REGISTERED LIMITED LIABILITY PARTNERSHIP
600 CONGRESS AVENUE, SUITE 2400
AUSTIN, TEXAS 78701-3271
WWW.FULBRIGHT.COM

DAVID L. PARKER
PARTNER
DPARKER@FULBRIGHT.COM

DIRECT DIAL: (512) 536-3055
TELEPHONE: (512) 474-5201
FACSIMILE: (512) 536-4598

April 12, 2004

Corres. and Mail
BOX AF

CERTIFICATE OF MAILING
37 C.F.R 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date below:

April 12, 2004 — Date
David L. Parker

MS AF
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Re: *SN 09/982,113 entitled "A METHOD TO INCORPORATE N-(4-HYDROXYPHENYL) RETINAMIDE IN LIPOSOMES" by Lopez-Berestein et al.*
Our ref: UTSC:660US Client ref: MDA00-030

Commissioner:

Please find enclosed:

1. Amendment and Response to Office Action Dated February 20, 2004
2. Supplemental Information Disclosure Statement (with Form PTO-1449 and reference A57);
3. Copy of foreign search report; and
4. A postcard to acknowledge receipt of these materials. Please date stamp and mail this postcard.

Should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/UTSC:660US.

Very truly yours,

David L. Parker
Reg. No. 32,165

DLP/lb
Enclosures
25404428.1 / 10109798